

New Claims 28-47

Support for claims 28-47 can be found in the Specification on pp. 8-15, Examples 1, 3, 4, 6-9, and 11-14. Additional support for claim 28 is found in the Specification on p. 5, lines 20-29; for claims 29-32 on p. 5, lines 14-19; for claims 36-39 on p. 5, line 31- through p. 6, line 2; for claims 40-43 on p. 5, lines 9-19; and for claims 44-47 on p. 5, lines 20-29, pp. 8-15, Examples 1-14, and p. 6, lines 14-17.

Claim Rejections - 35 USC § 103(a)

The Examiner has rejected claims 1-27 under 35 U.S.C. § 103(a) as being unpatentable over Haytko et al. in view of Horvath, C. (J. Chromatography Library), for reasons of obviousness. The Office Action states on p. 3, last para.: “The process[es] taught by Haytko et al. are similar processes of applicant’s claims.” And “Although Haytko et al is silent about the use of a displacer ... in analogous art Horvath et al teach that the term chromatography (HPLC and displacement) has become synonymous...” *Id.* p. 3, last line through p. 4, 2nd line.

Applicants respectfully submit that the Examiner has misinterpreted what Horvath teaches. The page in Horvath cited in the Office Action, (p. 179, lines 1-4) states that “...the term chromatography has become synonymous with *linear elution chromatography*.” Emphasis added. The Examiner’s misinterpretation can readily be seen by reading just one sentence further in Horvath where it is stated that “...most chromatographic texts ... have ignored displacement development, *the other mode of chromatography*” *Id.*, lines 5-7, emphasis added.

Then, on p. 180, lines 9-13, Horvath goes on to say “In principle, the technique [displacement chromatography] is analogous to isotachophoresis ... based on competition ... for adsorption sites ... *and the process is therefore nonlinear*.” Emphasis added. Horvath continues, stating “Progress in this field has also been impeded by the theory of non-linear chromatography being more complicated than that of linear elution chromatography and the paucity of experimental support” *Id.*, lines 15-17.

Later, on p. 186, last paragraph, Horvath states: “There are several sudden changes in the mobile phase composition in displacement development, *so that the process consists of distinct steps unlike that of elution chromatography*.” Emphasis added.

In light of such statements, Applicants respectfully submit that displacement chromatography, a non-linear step process, is not synonymous with elution chromatography (i.e. HPLC), a linear process. Not only is displacement chromatography not synonymous with linear elution chromatography, it is in fact very different from linear elution, and it is not obvious to replace linear elution chromatography with step-wise displacement chromatography, as plainly stated by Horvath.

For example, Horvath states, on p. 190, under the sub-heading **Displacer**, that "... the selection of a suitable displacer may represent the greatest obstacle at present because of the paucity of experience in this regard." Further, Horvath states that "... wide use of displacement development is greatly hampered by lack of sufficiently broad experience and data base," *Id.*, p. 200, second para. And lastly, "It is expected that scaling up ... in the displacement mode will require more careful engineering than that employed presently is elution chromatography." *Id.*, last para.

As discussed in the previous Response A, filed May 13, 2002, for a *prima facie* case of obviousness, there must be some suggestion or motivation, either in the references themselves or in the knowledge generally available to one of ordinary skill in the art to modify the reference, there must be a reasonable expectation of success, and the cited art must teach or suggest all the claim limitations. All three criteria must be met or there is no *prima facie* case.

In the instant case, the first criterion, the motivation to modify, is not taught in Haytko et al., and is not present in the knowledge generally available to one of ordinary skill in the art, even in light of Horvath. Contrary to what is stated in the Office Action, Applicants respectfully submit that Horvath provides convincing evidence that the two chromatographic methods - linear elution chromatography (including HPLC) and non-linear displacement chromatography - are not synonymous, are not interchangeable, and that much optimization and "more careful engineering" are required to successfully employ displacement chromatography, assuming the "greatest obstacle" of finding a suitable displacer can be overcome.

The second criterion, a reasonable expectation of success, is also not taught by Haytko et al., nor present in the knowledge generally available in the relevant art. As stated in Horvath, "In the design of displacement development the selection of a suitable displacer may represent the greatest obstacle The displacer must meet several stringent requirements:...." Horvath, p. 190, lines 7-10. And later, "Displacement

chromatography falls short of simple measures of column efficiency and resolution germane to linear elution chromatography....” *Id.*, p. 192, lines 8-10. Applicants respectfully submit that if displacement chromatography falls short of simple measures of column efficiency and resolution germane to linear elution chromatography, there can be no expectation that simply replacing one method with the other will prove successful in achieving similar efficiency and resolution.

Similarly, Horvath even goes so far as to state that “Attempts in our laboratory to separate biopolymers by displacement chromatography with columns traditionally used in HPLC ... were not yet successful.” *Id.*, p. 200, lines 10-12.

Like the first and second criteria, the third criterion is also not satisfied. Haytko et al., with Horvath, do not teach or suggest all the claim limitations of the present invention. As stated in Horvath, the “greatest obstacle” in displacement chromatography is finding a suitable displacer. Claim 1 of the present invention requires a process for obtaining a HMG-CoA reductase inhibitor wherein one of the steps in the process includes displacement chromatography and “... involves using a displacer for displacing the HMG-CoA reductase inhibitor.” Nothing in Haytko et al. or Horvath provides any insight into how one could find a suitable displacer for displacing HMG-CoA reductase inhibitors. Haytko et al. do not discuss or suggest displacement chromatography. Horvath does not discuss or suggest how to find a displacer for HMG-CoA reductase inhibitors. In fact, Horvath states that “The displacer must meet several stringent requirements: (i) it has to have greater affinity to the stationary phase than any of the feed components; (ii) it should be readily available in the carrier solvent; (iii) it should not interact with the feed components; (iv) it should be easily removable.... [and it must have] the general requirements of low toxicity and viscosity....” Horvath, p. 190, lines 9-16.

Applicants respectfully submit that the lack of even one of the three criteria is enough to overcome a *prima facie* case of obviousness. In the instant case, none of the three criteria is present.

New Product-by-Process Claims 28-43

Regarding product-by-process claims 28-43, Table 1 below shows the overall purity of pooled fractions of HMG-CoA reductase inhibitors after purification by displacement chromatography, obtained according to the process of the instant invention,

in comparison to the purity of the crude input HMG-CoA reductase inhibitors prior to purification by displacement chromatography. Purities of the inhibitors either prior to or after purification by displacement chromatography were determined by analytical HPLC analysis.

Table 1

<u>Example No.</u> (from the description of the instant invention)	<u>HMG-CoA reductase inhibitor</u> (to be purified by a process of the instant invention)	<u>INPUT HMG-CoA Reductase Inhibitor</u> (Overall purity, expressed as Area % of HMG-CoA reductase inhibitor)	<u>OUTPUT HMG- CoA Reductase Inhibitor</u> (Overall purity, expressed as Area % of HMG-CoA reductase inhibitor from pooled fractions)
EXAMPLE 1	Pravastatin sodium salt	88	99.8
EXAMPLE 2	Pravastatin sodium salt	88	99.7
EXAMPLE 3	Pravastatin sodium salt	88	99.8
EXAMPLE 4	Pravastatin sodium salt	88	99.8
EXAMPLE 5	Pravastatin lactone	85	99.7
EXAMPLE 6	Pravastatin lactone	85	99.8
EXAMPLE 7	Pravastatin lactone	85	99.8
EXAMPLE 8	Pravastatin lactone	85	99.8
EXAMPLE 9	Simvastatin l lactone	87	99.8
EXAMPLE 10	Simvastatin lactone	87	99.7
EXAMPLE 11	Simvastatin lactone	87	99.8
EXAMPLE 12	Lovastatin lactone	87	99.9
EXAMPLE 13	Lovastatin lactone	87	99.8
EXAMPLE 14	Mevastatin lactone	85	99.8

There are significant differences between the product obtained by the Haytko et al. purification process and the product obtained according to the purification process of the instant invention. First, the product of the instant invention is purified from a crude inhibitor using displacement chromatography as the only purification step in the process, and the HPLC purity of any given HMG-CoA reductase inhibitor is determined from the pooled fractions eluting directly from the displacement chromatography column (see Table 1.) In contrast, the product obtained by Haytko et al. is obtained by a purification process which comprises HPLC purification, followed by crystallization, filtration and drying. These additional steps after the HPLC purification step further contribute to the claimed purity of the Haytko et al. products.

Second, Haytko et al. do not use, or suggest using, displacement chromatography, a step-wise chromatography system, to purify the disclosed HMG-CoA reductase inhibitors. Haytko et al. use HPLC chromatography, a linear elution system, combined with additional crystallization, filtration and drying steps. As discussed above, displacement chromatography is very different from HPLC chromatography, not the least because it one must identify a suitable displacer, particular to the product to be purified, for the displacement chromatography to be successful.

Third, the overall purity of HMG-CoA reductase inhibitors is very important in the pharmaceutical industry, as is the overall purity of any pharmaceutical agent. Numerous complex processes are employed in the purification of pharmaceutical agents, with the primary goal of producing a 'pure' substance. The purity of a drug substance is an essential factor in ensuring quality control and drug safety. The "International Conference on the Harmonization of the Technical Requirements for Registration of Pharmaceuticals for Human Use" (ICH) sets a framework with guidelines for achieving the standardization of registration procedures. Impurities are an important topic in the ICH guidelines, and thresholds are given for the reporting, quantification and identification of impurities. For example, according to the ICH guidelines all pravastatin impurities higher than 0.05% must be monitored and impurities at levels of 0.10% or higher must be identified.

In the instant application, increasing the HPLC purity of pravastatin sodium salt from 99.5% to 99.7% is a 0.2% absolute increase in purity. But relative to the 99.5% pure product, the 99.7% pure product contains effectively 40% less impurities. Achieving such high levels of drug purity is extremely challenging and complicated, especially as

one approaches the maximum purity of 100%. For example, increasing the purity in a given drug from 99.5% to 99.7% is a far more difficult and complicated task than increasing the purity from 99.3% to 99.5%, although in both cases the difference in impurities content is the same, namely in the range of 0.2%.

Various factors play a role in this phenomenon. Sometimes certain impurities co-purify with the product, and are extremely difficult to remove. In other cases, for example in HPLC purifications, limits in peak resolution, impurity detection, and column efficiency contribute to the plateau effect seen in purification limits.

In the present case, the content of specific impurities in the pooled fractions of the HMG-CoA reductase inhibitors, obtained after displacement chromatography according to the instant invention, was performed (see Table 2). This determination showed that certain impurities were surprisingly removed very efficiently by the process of the instant invention, in comparison to the teaching of Haytko et al. Haytko et al. do not teach such high levels of overall purity of HMG-CoA reductase inhibitor in a pooled fraction, nor do they teach such a high level of purity in a pooled fraction with respect to specific impurities commonly found in specific HMG-CoA reductase inhibitors, namely the lactone impurity content and epi-prava impurity content of "purified" pravastatin sodium salt.

Table 2

<u>Sample and Experiment No.</u>	INPUT (crude pravastatin sodium salt)			OUTPUT (pooled fraction of pravastatin sodium salt)		
	<u>Pravastatin sodium salt</u>	<u>6-Epiprava content</u>	<u>Lactone content</u>	<u>Pravastatin sodium salt</u>	<u>6-Epiprava content</u>	<u>Lactone content</u>
	(overall purity, in area %)	(area %)	(area %)	(overall purity, in area %)	(area %)	(area %)
PD 21	89.39			99.85		
		7.90			0.02	
			1.13			0.04
PD 22	89.39			99.83		
		7.90			0.02	
			1.13			0.05
PD 23	89.36			99.90		
		7.93			0.03	
			1.12			0.04
PD 24	89.47			99.76		
		8.05			0.05	
			1.16			0.03

In summary, the product obtained by Haytko et al. and that obtained by the present invention must be compared at the same stage of purification, i.e. after chromatography. Haytko et al. report purities of HMG-CoA reductase inhibitors of $\geq 99.5\%$, but they do not determine such purities until after the subsequent crystallization, filtration and drying steps which follow the HPLC chromatographic purification step. Applicants respectfully submit that compared to the post-chromatography product of the instant invention, the post-chromatography product of Haytko et al. contains elevated levels of impurities, relative to what is reported. The results of the present invention are surprising and unexpected, given the inability of HPLC chromatography methods to remove such impurities, unless additional post-chromatographic purification steps such as crystallization, filtration, and drying are added to the process.

New Process Claims 44-47

Regarding new process claims 44-47, the present invention is the first to show successful use of a single purification step - displacement chromatography - for the purification of HMG-CoA reductase inhibitors. In the claimed process of the present invention, a crude sample of inhibitor is fed onto an appropriate column such that the HMG-CoA reductase inhibitor adsorbs to the column material, a displacer is introduced onto the column to displace the adsorbed HMG-CoA reductase inhibitor, and pooled fractions containing purified HMG-CoA reductase inhibitor are then obtained by this single purification step. Claims 45-47 further require an HPLC purity level exceeding 99.7%. Use of displacement chromatography has never been successfully reported for the purification of HMG-CoA reductase inhibitors prior to the method disclosed in the present application, nor has anyone reported identification of a suitable displacer for use in purification of such compounds.

In addition, no one has reported purification of HMG-CoA reductase inhibitors from a crude fraction to a final purified product having HPLC purity exceeding 99.7%, in a single purification step. Such a process is novel, and as argued above, not obvious in view of the prior art because of the inherent difficulties associated with displacement chromatography. For example, such difficulties as those associated with identifying a suitable column, and especially with identifying a suitable displacer. Applicants respectfully submit that new process claims 44-47 are therefore patentably distinct from the prior art, and are in condition for allowance.

CONCLUSION

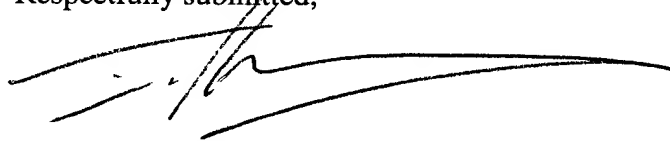
For the reasons set forth above, it is submitted that all pending claims are in condition for allowance. Reconsideration of the claims and a notice of allowance are therefore requested.

Applicant respectfully requests a two-month extension of time; however, this conditional petition for an additional extension of time is being made in the event that the need for an additional extension has been overlooked. Please pay any fees required for the timely consideration of this application from deposit account number 19-4972. The Examiner is requested to telephone the undersigned if any matters remain outstanding so that they may be resolved expeditiously.

Attached hereto is a marked-up version of the changes made to the claims by the current amendment, captioned "Version with Markings to Show Changes Made."

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Respectfully submitted,



Timothy M. Murphy
Registration No. 33,198
Attorney for Applicants
Bromberg & Sunstein LLP
125 Summer Street
Boston, Massachusetts 02110-1618
Tel: (617) 443-9292
Fax: (617) 443-0004

Version with Markings to Show Changes Made

5. (twice amended) A process according to claim 4, characterized in that the purified HMG-CoA reductase inhibitor is obtained by
- d1) collecting [the] fractions[,]; and
 - d2) analyzing the fractions with analytical HPLC and pooling the fractions depending on the quality of purity.